

### **REMARKS/ARGUMENTS**

With entry of this amendment, claims 31, 33 and 35-38 are pending in the instant application. The specification is amended to update the priority information as well as to correct an obvious typographical error in the legend of Figure 17. In addition, claims 32 and 34 are canceled without prejudice or disclaimer and claim 31 is amended as set forth in detail below. No new matter is added by these amendments. Applicants reserve the right to pursue any canceled subject matter in a related, co-pending application.

#### **Amendments to the Specification**

The paragraph beginning at the first line of the specification has been amended to indicate that U.S. Application Nos. 09/645,432 and 09/255,397 have issued as U.S. Pat. Nos. 6,656,449 and 6,299,858, respectively. This amendment merely updates the priority information and no new matter is added.

The legend to Fig. 17 has been amended to insert the reference character "C." between "and" and "72 hp.f." in order to correct an obvious typographical error omitting the reference character. Support for the amendment is provided in Figure 17. Because this amendment merely corrects an obvious clerical error, no new matter is added by this amendment.

#### **Claim Amendments**

Claim 31 has been amended to recite the claimed method with greater particularity by specifying that the method further includes screening the agent for a "desired activity" by "assessing whether the agent is effective to promote the desired activity in the teleost." Support for these amendments is found in the specification as filed at, *e.g.*, page 31, lines 24 & 25; and page 65, lines 7-21.

Claim 31 has also been amended to recite the claimed method with greater particularity by specifying that the detection is a change in expression of a protein or mRNA in a

specific organ or tissue of the teleost is "relative to the expression of the protein in the specific organ or tissue of a teleost to which the agent has not been administered." Support for this amendment is found in the specification at, *e.g.*, page 75, lines 7-9.

In addition, claim 31 now specifies that the detection step is performed *in vitro* or *in situ*. Support for this amendment is found in the specification at, *e.g.*, page 76, lines 25 to page 77, line 26; and page 80, line 16 to page 85, line 2, which generally describe measurement of mRNA or protein levels in teleost cells, tissues, or organs comprising extraction of mRNA or protein (exemplary *in vitro* methods) or by various *in situ* techniques for detection of mRNA or protein, including *in situ* hybridization, colorimetric staining procedures based on enzyme expression, or the use of antibodies in immunohistochemical procedures.

Claim 31 has also been amended for the sake of consistency of terminology and clarity by replacing "a response" with the phrase, "the change in expression," thereby maintaining explicit antecedence with the previous use of the phrase "a change in expression." Claim 31 has been further amended for clarity by deleting "the" before the phrase "at least one tissue or organ of the teleost."

Claims 32 and 34 have been canceled without prejudice or disclaimer.

These amendments are made for the sake of further expediting prosecution of this application and should not be construed as an acquiescence to any rejection.

### **Objections to the Disclosure and Drawings**

The Examiner objected to the disclosure because the priority information requires updating. Applicants have amended the paragraph beginning at the first line of the specification to indicate that U.S. Application Nos. 09/645,432 and 09/255,397 have issued as U.S. Pat. Nos. 6,656,449 and 6,299,858, respectively.

The Examiner objected to the drawing Figure 17 because it includes a Fig. 17C that is not mentioned in the brief description of the figure in the specification. Applicants have amended the legend to Fig. 17 to add the reference character "C."

In view of the above amendments, withdrawal of these objections is respectfully requested.

### **Priority**

The Examiner denied Applicant's claim for benefit of an earlier filing date under 35 U.S.C. 119(e), and granted an effective filing date for the pending claims of February 22, 1999. In particular, the Examiner alleges that screening for an agent for toxicity in a teleost detecting a change in expression of a protein or mRNA is not supported by either of U.S. Provisional Application Nos. 60/075,783 (the '783 application), filed February 23, 1998, or 60/100,950 (the '950 application), filed September 18, 1998. Applicants respectfully request that the Examiner reconsider the priority claim for at least the reasons set forth below.

The '783 application discloses a method of screening an agent for an activity in zebrafish by detecting a change in expression of alkaline phosphatase (AP) by staining (*see* page 4, last paragraph). One type of activity disclosed in the '783 application is toxic activity (*see* page 5, fifth full paragraph). Two agents, fumagillin and ovacillin, are disclosed as having toxic effects, which are detected, at least in part, by AP staining of zebrafish embryos (*see* Figure 1 and page 6, second and third full paragraphs). Therefore, the disclosure of the '783 application provides clear support for a method as recited in the present claims.

### **Rejections under 35 U.S.C. § 112, first paragraph**

#### **Claims 31, 33, and 35-38**

Claims 31, 33 and 35-38 stand rejected as allegedly lacking enablement. In particular, the Examiner alleges that specification does not reasonably provide enablement for

the claimed method wherein the expression of protein or mRNA (i) is detected *in vivo*, or (ii) is performed without a control for comparison. This rejection has been rendered moot by amending claim 31 as follows.

First, the claims as amended do not recite that the expression of protein is detected *in vivo*. To further expedite prosecution of the instant application, Applicants have amended claim 31 to recite that the detecting step is performed *in vitro* or *in situ*, thereby obviating part (i) of the enablement rejection.

Second, claim 31 has been amended to include a comparison of the expression of mRNA or protein in the agent-treated teleost with a control teleost to which the agent has not been administered, thereby obviating part (ii) of the enablement rejection.

Claims 31 and 34

Claims 32 and 34 stand rejected as allegedly lacking enablement. In particular, the Examiner alleges that the specification fails to teach how to monitor protein or mRNA activity in a single embryo over time. This rejection has been rendered moot by canceling claims 32 and 34. The cancellation of these claims should not be construed as acquiescence to any ground of rejection.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 31-38 stand rejected as allegedly being indefinite. In particular, the Examiner alleges that claim 31 (i) is unclear because it refers to a "change in expression" without setting forth a basis for determining the change, (ii) is unclear because "a response" is not definitely linked to "a change in expression", and (iii) recites the limitation "the at least one tissue or organ" without antecedent basis. Regarding claim 32, the Examiner alleges that it is unclear whether the terminology "detected over time" is meant to include multiple sampling of a particular teleost over time or that toxic activity is not detectable until a period of time has passed. Regarding claim 34, the Examiner alleges that it is unclear whether the toxic activity is

measured at intervals over a period of time or if the toxic activity occurs at intervals over a period of time.

Claim 31 has been amended to (i) include a comparison of the expression of protein in the agent-treated teleost with a control teleost to which the agent has not been administered, (ii) clarify that a "response" refers to a "change in expression", and (iii) delete "the" before " at least one tissue or organ of the teleost, thereby obviating the indefiniteness rejection as applied to claim 31.

Claims 32 and 34 have been canceled, thereby rendering moot the indefiniteness rejection as applied to these claims.

These amendments should not be construed as acquiescence to any ground of rejection. In view of these amendments set forth above, withdrawal of the present indefiniteness rejection is respectfully requested.

### **Rejections under 35 U.S.C. § 102**

Claims 31-35 stand rejected as allegedly anticipated by Mizell (*Int. J. Dev. Biol.* 41:411-423, 1997).

This rejection is traversed in part and overcome in part. The claims as presently amended recite a "method of screening an agent for toxic activity and a desired activity *in vivo*" and require the additional step of "assessing whether the agent is effective to promote the desired activity in the teleost." Mizell does not disclose or suggest such a method as presently recited in claim 31. Mizell is concerned with the use of a zebrafish embryo as a "sentinel" for aquatic pollution, in particular for determining whether a pollutant is a health or environmental hazard. (See Mizell at, *e.g.*, Abstract.) Mizell does not discuss or otherwise suggest the use of zebrafish or other teleosts for also determining whether an agent promotes a desired (*e.g.*, therapeutic) activity.

Accordingly, for at least the reasons above, the present claims are novel over Mizell. Withdrawal of the rejection is respectfully requested.

**Rejections under 35 U.S.C. § 103**

Claims 36-38 stand rejected as allegedly obvious over Mizell as applied to claims 31-35 and further in view of Terse (*Toxicon* 31:913-919, 1993).

This rejection is traversed in part and overcome in part. As discussed above, Mizell does not disclose or suggest a method as presently recited in the amended claims at least for the reason that Mizell does not disclose or otherwise suggest screening an agent in a teleost for a desired activity. Terse does not cure this deficiency of Mizell. Terse discusses screening of mycotoxin agents for toxic activity *in vitro* in cultured mammalian cells in 96-well multi-well plates. There is no teaching or suggestion in Terse, however, to screen an agent for a desired activity in a teleost.

Accordingly, for at least the reasons above, a *prima facie* case of obviousness has not been established with respect to the present claims. Withdrawal of the present rejection is respectfully requested.

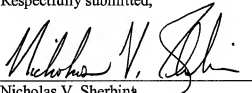
**CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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Nicholas V. Sherbina  
Reg. No. 54,443

TOWNSEND and TOWNSEND and CREW LLP  
Two Embarcadero Center, Eighth Floor  
San Francisco, California 94111-3834  
Tel: 206-467-9600  
Fax: 206-623-6793  
NVS:jae  
60970051 v1